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Prevalence of Iron Deficiency and its Sociodemographic Patterning in Indian Children and Adolescents: Findings from the Comprehensive National Nutrition Survey 2016–18

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ABSTRACT

Background: Anemia control programs in India focus mainly on the measurement of hemoglobin in response to iron–folic acid supplementation. However, representative national estimates of iron deficiency (ID) are not available.

Objectives: The objective of the present study was to evaluate ID prevalence among children and adolescents (1–19 y) using nationally representative data and to examine the sociodemographic patterning of ID.

Methods: Cross-sectional data from the Comprehensive National Nutrition Survey in children (1–4 y: $n = 9635$; 5–9 y: $n = 11{,}938$) and adolescents (10–19 y; $n = 11{,}507$) on serum ferritin (SF) and other biomarkers were analyzed to determine inflammation-adjusted ID prevalence [SF (μg/L): <12 in 1–4 y and <15 in 5–19 y] and its relation to sociodemographic indicators. Multiple-regression analyses were conducted to identify the exposure associations of iron status. In addition, the relation between SF and hemoglobin was assessed as an indicator of iron utilization in different wealth quintiles.

Results: ID prevalence was higher in 1- to 4-y-old children (31.9%; 95% CI: 31.0%, 32.8%) and adolescent girls (30.4%; 95% CI: 29.3%, 31.5%) but lower in adolescent boys and 5- to 9-y-old children (11%–15%). In all age groups, ID prevalence was higher in urban than in rural participants (1–4 y: 41% compared with 29%) and in those from richer quintiles (1–4 y: 44% in richest compared with 22% in poorest), despite adjustment for relevant confounders. SF significantly interacted with the wealth index, with declining trends in the strength of association between hemoglobin and SF from the richest to the poorest groups suggesting impaired iron utilization for hemoglobin synthesis in poorer wealth quintiles.

Conclusions: ID prevalence was indicative of moderate (in preschool children and adolescent girls) or mild (in 5- to 9-y-old children and adolescent boys) public health problem with significant variation by state and age. Focusing on increasing iron intake alone, without addressing the multiple environmental constraints related to poverty, may not result in intended benefits. *J Nutr* 2021;151:2422–2434.

Keywords: adolescents, anemia, children, hemoglobin, inflammation, iron folate, India, iron deficiency, serum ferritin, sTfR

Introduction

Iron deficiency (ID) and associated anemia have serious adverse consequences for human capital development with associated impacts on morbidity and mortality in women and children, impaired cognition in children, and decreased physical work capacity in adults (1). The recent Comprehensive National Nutrition Survey (CNNS) in India has shown anemia prevalence to be ~40% among 1- to 4-y-olds, ~23% among 5- to 9-y-olds, and ~28% among adolescents (2).

Anemia is known to be multifactorial in its etiology, with causes including specific nutritional deficiencies (of iron, folic acid, vitamin B-12, vitamin A, riboflavin, pyridoxine, zinc, copper), infections, hemoglobinopathies, as well as inflammation related to chronic disease (3). However, similarly to other developing countries, anemia control programs in India, since

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their initiation in 1970, have continued to revolve around iron–folic acid (IFA) supplementation, because ID is still considered to be the major cause of anemia (4). However, analyses from the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project suggest that the contribution of ID as a cause of anemia may be lower in countries with high underlying infection burden than in those with low infection burden (5).

Nationally representative data on the prevalence of ID and its relation to hemoglobin in vulnerable population groups are vital for planning rational and effective interventions for ID-associated anemia. This is particularly important for India, where high prevalence of anemia persists despite IFA supplementation programs having been ongoing for almost 5 decades. This low impact is partly due to poor compliance to the supplementation and supply-related problems (6) and possibly due to the deficiency of other erythropoietic nutrients. It might also be due to a lower prevalence of ID than is assumed. Concerns have also been raised about the potentially deleterious impact of iron supplementation in non-iron-deficient individuals due to associated oxidative stress and increased risk of infections (7).

Hitherto, large-scale surveys in India measured hemoglobin alone, which was used as a proxy for iron status; but it is neither sensitive nor specific for this purpose (8). Iron status indicators were not usually included owing to their high cost as well as technical difficulties in analysis. However, the recent CNNS, conducted in 30 states of India during 2016–2018, is uniquely positioned to address this knowledge gap by providing data on inflammation-adjusted iron status indicators in children and adolescents (aged 1–19 y). We used these nationally representative data of robust ID indicators to analyze its prevalence in children and adolescents. We also examined the social patterning of ID and its relation to hemoglobin, along with exposure associations to explain these patterns.

Methods

Study population and sampling design

The CNNS (2016–18) is the first ever nationally representative nutrition survey of children and adolescents in India. The survey was conducted under the leadership of the Ministry of Health and Family Welfare, Government of India in collaboration with UNICEF and the Population Council. The methodological details of the survey are available in the CNNS report (9). Briefly, the CNNS collected data from preschool children (0–4 y old), school-age children (5–9 y old), and adolescents (10–19 y old) in all 30 states of India using a multistage, stratified, probability proportional to size (PPS) survey design covering rural and urban households. The first stage was the selection of rural and urban primary sampling units (PSUs) using PPS sampling and the second stage was a systematic random selection of households within each PSU. In large PSUs, the sampling design involved 3 stages, with the addition of a segmentation procedure to reduce enumeration areas to manageable sizes. Households with individuals aged 0–19 y were randomly selected from the PSUs followed by stratification of children and adolescents into 3 strata (0–4 y, 5–9 y, and 10–19 y). Only 1 child or adolescent was selected from each age group per household. For biological sampling, 50% of all the children >1 y of age who completed anthropometry were selected by systematic random sampling. Children and adolescents with physical deformity, cognitive disabilities, chronic illness, acute febrile or infectious illness, acute injury, ongoing fever, and pregnancy were excluded.

Ethical approvals

Ethical approvals were obtained from the Population Council's international review board, New York, and from the Post Graduate Institute of Medical Education and Research, Chandigarh, India. For children <10 y old, informed consent was obtained from parents or caregivers; for adolescents aged 11–17 y, informed consent of a parent or caregiver as well as assent from the participants were obtained; participants aged 18–19 y provided informed consent for themselves. In cases of illiterate consenting persons, a thumb impression was taken in the presence of a witness.

Data collection

Information on sociodemographic characteristics of the household and anthropometric data of participants (1 child or adolescent per age group per household) were collected using standardized procedures. The wealth index was computed based on the ownership of common household items and facilities, adopting a standardized method (10). Information was also collected on the use of health facilities and access to social entitlements. Access to facilities like drinking water, handwashing, and sanitation was categorized based on WHO/UNICEF Joint Monitoring Programme for Water Supply, Sanitation and Hygiene guidelines (11). Information was also collected on supplemental IFA intake in the previous week as well as frequency of consumption of key food items in the past 7 d in all age groups. Age- and sex-standardized *z* scores were calculated for height-for-age, weight-for-height (WHZ), weight-for-age, and BMI-for-age (BMIAZ) using the WHO Growth Reference (12, 13) and for triceps skinfold thickness-for-age using reference curves based on US children and adolescents (14).

Biological sample collection and analyses

Venous blood samples were collected from selected children and adolescents by trained phlebotomists. A day before sample collection, parents and children (if possible) were instructed to ensure an overnight fast of 8–10 h. During the collection of venous blood samples by trained phlebotomists, binary information (yes/no) on fasting status and the time of sample collection were recorded. Almost all the samples (>99%) were collected in the morning and provided information about the fasting status. The blood samples were collected in trace-element-free tubes using a standard protocol; serum was separated and stored frozen for analysis. Biochemical analyses were carried out by SRL Labs (Mumbai, Gurugram, and Kolkata). A 5-part automated cell counter (Beckman Coulter, LH 750 Hematology analyzer) was used for the estimation of hemoglobin concentration, by photometric estimation with the cyanmethemoglobin method, in venous whole-blood samples. The hemoglobin concentrations were adjusted for altitude in enumeration areas at >1000 m of altitude. Serum ferritin (SF) was estimated by the direct chemiluminescence 2-site sandwich

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Abbreviations used: AGP, α-1-acid glycoprotein; BIS, body iron stores; BMIAZ, BMI-for-age *z* score; BRINDA, Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia; CNNS, Comprehensive National Nutrition Survey; CRP, C-reactive protein; ID, iron deficiency; IFA, iron–folic acid; PPS, probability proportional to size; PSU, primary sampling unit; SES, socioeconomic status; SF, serum ferritin; sTfR, serum transferrin receptor; WASH, water, sanitation, and hygiene; WHZ, weight-for-height *z* score.

immunoassay method (Centaur, Siemens Healthcare Diagnostics). C-reactive protein (CRP) and serum transferrin receptor (sTfR) concentrations were estimated by particle-enhanced immunonephelometry (BNII, Siemens). Serum retinol was measured using reverse-phase HPLC; RBC folate and serum vitamin B-12 were measured by competitive immunoassays using direct chemiluminescence (Siemens Centaur); serum triglycerides were measured by enzymatic assay of lipoprotein lipase using spectrophotometry. Rigorous quality control procedures were implemented during sample collection, transportation, and testing using standard internal and external (US CDC) quality assurance procedures (9). First, an internal quality control sample was used for each batch of 20 survey samples. Second, for external quality assurance, ~5% of the samples were tested for analytical concordance with the main analytical laboratory at the All India Institute of Medical Sciences, Delhi. Third, on a weekly basis, a percentage of samples were split and reanalyzed. Detailed reporting of quality assurance data for the iron biomarkers and CRP assays is, however, not available.

Anemia was diagnosed using WHO cutoffs of hemoglobin concentration (g/dL): <11.0 (1–4 y), <11.5 (5–11 y), <12.0 (12–14 y), <12.0 (15–19 y, girls), and <13.0 (15–19 y, boys) (15). The cutoffs for diagnosing high serum triglycerides (mg/dL) were ≥100 (5–9 y) and ≥130 (10–19 y) (16).

Definition of ID

Because inflammation is likely to influence the indicators of ID (SF and sTfR) in different directions, resulting in underestimation and overestimation of ID, respectively, this can affect the ID prevalence estimate. Therefore, we attempted 3 different adjustments to account for inflammation: *1*) exclusion of participants with inflammation (indicated by CRP >5 mg/L) followed by the use of the WHO-recommended age-specific cutoff of <12 μg/L in the 1–4 y age group and <15 μg/L in the 5–19 y age group (17); *2*) using higher cutoffs of SF in participants with evidence of inflammation as recommended by the WHO (<30 μg/L in the 1–4 y age group and <70 μg/L in the 5–19 y age group) (18); and *3*) adjusting for the CRP concentration by the probability method of correction for inflammation (19), which is a modification of the BRINDA correction approach (20, 21). This latter approach was needed because the CRP measurements in the CNNS were performed with 2 different kit-based methods of varying resolution, where 1 high-resolution method had a limit of detection of 0.2 mg/L, whereas the equivalent value for the other method was 3 mg/L (9). The majority of the measurements were made by the latter method. Briefly, the probability method of correction for inflammation was an extension of the BRINDA concept and used a Monte Carlo simulation-based regression technique that estimated the true probability distribution of SF accounting for random interindividual variability in SF, while eliminating any systematic component that could have been due to relatively deterministic processes such as infection/inflammation, which was measured by CRP. The ID prevalence was calculated from the area under the estimated probability distribution curve of SF across individuals below the defined cutoff for deficiency. The estimated probability distribution was adjusted for survey weight within the regression method.

ID prevalence estimates were also obtained using additional indicators: *1*) sTfR concentration ≥1.76 mg/L (kit-based cutoff); *2*) sTfR/SF index (calculated as sTfR/$\log_{10}$ferritin ≥1.63 in the 1–4 y age group and ≥1.49 in the 5–19 y age group; and *3*) body iron stores (BIS) <0 mg/kg. BIS were calculated using Cook's formula: BIS (mg/kg) = −[log10 (sTfR∗1000/SF) − 2.8229]/0.1207 (22, 23).

Statistical analyses

We used SPSS version 23.0 (SPSS Inc.) and R version 4.0.2 (R Core Team, 2020; https://www.R-project.org/) to conduct the statistical analyses. Sampling weights were used to ensure representativeness of the estimates at the national/state level because the samples were allocated to different sampling domains (states, urban and rural areas within states) in a disproportionate manner. The sampling weights were based on sampling probabilities calculated for each sampling stage (cluster and household levels). Sample weights were calculated for the 3 survey age groups and for the survey sample and biological sample at both the state and national levels and were used for all further analyses. The demographic characteristics of the sample included in the present study were compared with the same from the total CNNS survey sample as well as the largest biological sample (i.e., cases with hemoglobin values), to evaluate the potential bias resulting from nonresponse and missing data.

We examined the normality of the distributions by plotting histograms and boxplots and, when necessary, variables were log transformed to achieve normality. For biochemical values, we identified outliers as values deviating ±6 SDs from the group mean. We calculated the ID prevalence along with 95% CIs for the whole sample as well as in subsamples by states. We also conducted subgroup analyses to understand the urban–rural, age, and sex differentials in the prevalence of ID. The comparisons between groups were done by examining the overlap of 95% CIs. We compared the age-related differences in the ID prevalence in boys and girls graphically by nonparametric smoothed curves with 95% confidence bands. We also compared the ID prevalence in children classified as per the categories of anthropometry-based nutritional status, fasting/nonfasting status, as well as other sociodemographic variables such as wealth index; mothers' education; and water, sanitation, and hygiene (WASH) indicators. To better understand the influence of inflammation on the relation between ID and sociodemographic variables, we compared the mean (or geometric mean) values of ID indicators in groups with and without inflammation and evaluated the prevalence of elevated CRP in relation to the sociodemographic and WASH variables. Further, we conducted multiple linear regression analyses to understand the exposures associated with ID using each of its 2 indicators (SF and sTfR) as dependent variables. Separate models were developed for each of the 3 age groups. All significant associations of the iron biomarkers determined by stepwise regression analyses (with statistical significance for entry set at $P \leq 0.05$) were included in the final regression models. In addition, CRP was included as a continuous variable with adjustment for the censoring of lower concentrations. We in addition evaluated the interaction of SF with the wealth index using hemoglobin as a dependent variable after adjustment for all relevant confounders.

The main findings on ID prevalence (overall, state-wise, and prevalence in relation to age, sex, sociodemographic variables, WASH, and nutritional status indicators) are based on SF concentrations adjusted for inflammation by the modified BRINDA method. These analyses are based on a sample with all cases where values of SF and CRP were available. The same sample was used for assessing the interaction between SF and wealth index as a determinant of hemoglobin. For comparing the ID prevalence estimated by different indicators (SF, sTfR, sTfR/SF index, and BIS), a sample with participants having values of all 3 parameters (SF, sTfR, and CRP) was used after removing cases with high CRP concentrations, in order to have a common denominator. The same sample was used for multiple-regression analyses to assess the exposure associations of iron status by 2 indicators: SF and sTfR.

Results

Characteristics of the study population

A total of 105,243 children and adolescents (1–4 y: $n = 31,058$; 5–9 y: $n = 38,355$; 10–19 y: $n = 35,830$) were interviewed and had anthropometric data collected, of which paired data on SF and CRP measurements were available for 33,484 (~30%): children 1–4 y old: $n = 9635$; children 5–9 y old: $n = 11,938$; adolescents 10–19 y old: $n = 11,507$ (**Figure 1**). Paired data on sTfR and CRP, after excluding participants with high CRP (>5 mg/L), were available for 30,046 children and adolescents (1–4 y: $n = 8511$; 5–9 y: $n = 10,956$; 10–19 y: $n = 10,579$). The study sample (with paired SF and CRP) and the hemoglobin sample (with hemoglobin values) were similar in terms of participant characteristics including age, sex,

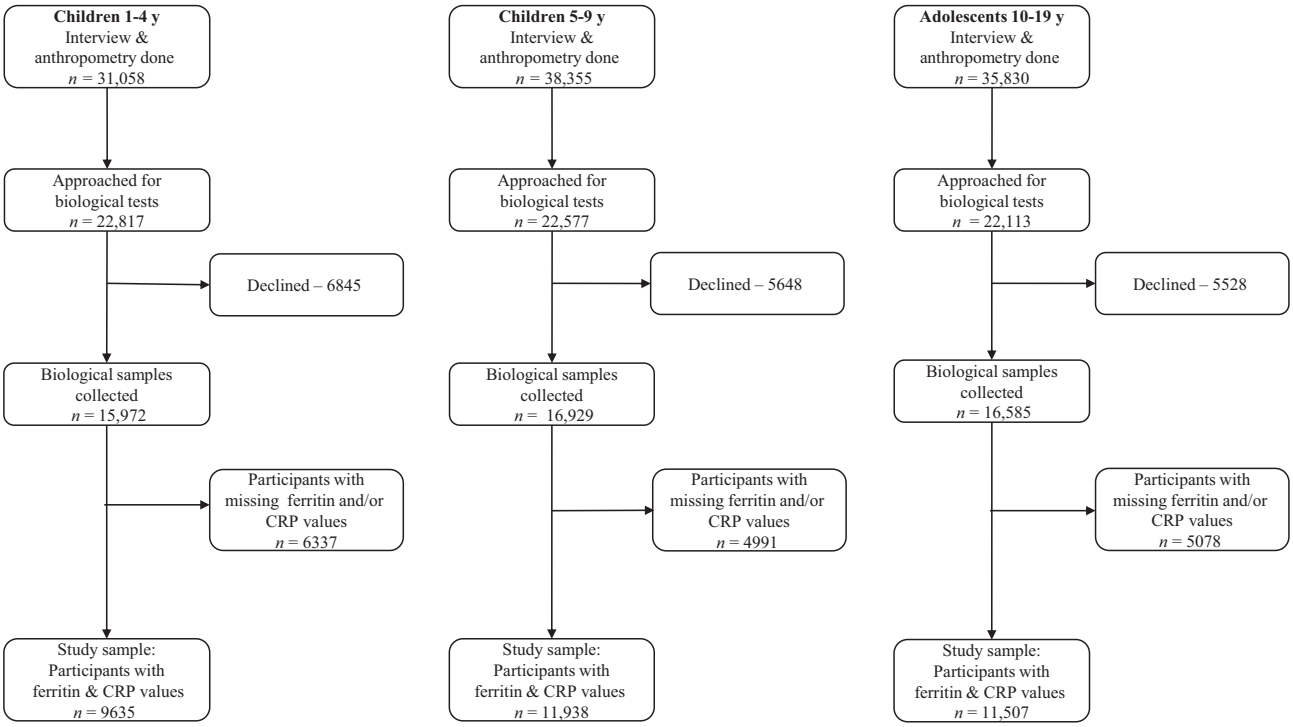

FIGURE 1 Study profile. The analytical sample included participants with serum ferritin and CRP values from the Comprehensive National Nutrition Survey 2016–18. CRP, C-reactive protein.

area of residence, caste, and wealth index. These characteristics were also similar to those in whom anthropometric data were collected (total sample), except that the proportion of 3- to 4-y-old children included in the study sample was higher than that of those aged 1–2 y (62% compared with 38%) (**Supplemental Table 1**).

In the 3 age groups, participants from the Eastern and North-Eastern regions ranged between 19% and 27% of the total sample, those from the Northern and Southern regions ranged between 15% and 21%, whereas those from the Central and Western regions ranged between 8% and 10%. **Table 1** presents age-specific general characteristics of the study population. Among 1- to 4-y-old children, ~35% were stunted, ~16% were wasted, and ~35% were underweight. Prevalence of anemia was ~40% in preschool children, ~23% in 5- to 9-y-old children, and ~29% in adolescents (**Table 2**). Consumption of an IFA supplement in the previous week was reported by <10% of children and adolescents, reflecting low availability or uptake of the supplementation. Although <5% of children and adolescents (5–19 y old) were overweight or obese, based on the criterion of triceps skinfold thickness 1 SD above the median, one-third of the 5- to 9-y-old children and 16% of adolescents had high serum triglyceride concentrations (Table 1). The majority of the 5- to 9-y-old children and adolescents (~90%) provided a fasting sample, but in the 1–4 y age group, this proportion was only 17%.

Prevalence of ID estimated by different methods

Table 2 presents the national-level ID prevalence and geometric means of SF values estimated by different methods of inflammation adjustment in boys and girls from the 3 age groups. In the 1–4 y age group, the ID prevalence after adjustment for inflammation using the modified BRINDA method did not differ from the prevalence estimated by the exclusion method of inflammation correction and was only slightly lower (by 1.1%) than the prevalence estimate using separate cutoffs for participants with inflammation. For the 5- to 9-y-old and 10- to 19-y-old children, the prevalence estimates, by the modified BRINDA method of inflammation adjustment, were marginally lower than by the exclusion method of inflammation correction (by 1.2% and 0.4%, respectively), and were lower than the estimates using separate cutoffs for inflammation by 4.3% and 2.6%, respectively.

Table 2 also includes the prevalence estimates of ID in the 3 age groups using the alternative indicators of sTfR, sTfR/SF index, and BIS. The ID prevalence using different indicators varied substantially, with much higher prevalence by the sTfR and sTfR/SF index criteria, and much lower prevalence by the BIS criteria, than when using the SF-based estimates (Table 2). These ID indicators were, however, significantly correlated with each other and with hemoglobin (**Supplemental Table 2**).

ID prevalence in different states

Figure 2 presents state-wise prevalence estimates of ID (adjusted for inflammation using the modified BRINDA method) in the 3 age groups, after arranging the states in descending order of per capita net state domestic product (24). There was wide variation in ID prevalence, with some states like Assam and Mizoram showing <10% prevalence, and states like Rajasthan, Punjab, Haryana, and Gujarat showing >60% prevalence in the preschool age group. ID prevalence was >20% [indicative of a moderate/severe public health problem as suggested by the WHO (18)] in 20 states in preschool children, in 13 states in 5- to 9-y-old children, and in 21 states for adolescents. Although no consistent pattern of ID prevalence in relation to the state income was observed, the prevalence was higher than the national average in many relatively richer states (e.g., Punjab, Haryana, Gujarat) and lower than the national average in the poorer states (e.g., Assam, Jharkhand, Bihar, Uttar Pradesh), in all age groups.

TABLE 1 Characteristics of the children and adolescents of the 3 age groups: Comprehensive National Nutrition Survey 2016–18[1]

Characteristics	1–4 y	5–9 y	10–19 y
n	9635	11,938	11,507
Age, y	2.8 (2.7, 2.8)	7.0 (7.0, 7.1)	14.3 (14.2, 14.4)
Male	52.4 (49.7, 55.0)	51.0 (49.1, 52.9)	49.8 (47.8, 51.7)
Rural residence	75.3 (71.6, 78.6)	76.4 (73.1, 79.4)	74.5 (70.9, 77.8)
Caste			
Scheduled caste	24.4 (21.7, 27.2)	24.4 (22.0, 27.0)	23.6 (21.2, 26.1)
Scheduled tribe	11.2 (9.2, 13.5)	11.2 (9.3, 13.3)	9.3 (7.8, 11.0)
Other backward castes	42.3 (39.3, 45.2)	41.9 (38.9, 45.0)	42.7 (39.8, 45.7)
Others	22.2 (19.8, 24.7)	22.6 (20.2, 25.1)	24.5 (22.1, 27.0)
Religion			
Hindu	80.4 (77.3, 83.1)	80.6 (77.8, 83.1)	80.9 (77.9, 83.5)
Muslim	14.6 (12.1, 17.6)	14.8 (12.5, 17.5)	14.7 (12.2, 17.6)
Christian	2.8 (2.1, 3.8)	2.6 (1.9, 3.6)	2.3 (1.5, 3.5)
Sikh	1.5 (1.1, 1.9)	1.3 (1.1, 1.7)	1.6 (1.2, 2.0)
Others	0.7 (0.4, 1.2)	0.7 (0.4, 1.2)	0.6 (0.4, 0.9)
Wealth index			
Poorest quintile	16.0 (13.8, 18.5)	17.2 (15.3, 19.2)	17.3 (15.1, 19.9)
Poor quintile	20.3 (17.5, 23.3)	21.2 (19.2, 23.4)	20.4 (18.6, 22.2)
Middle quintile	22.7 (20.7, 24.7)	21.5 (19.9, 23.2)	21.3 (19.7, 23.0)
Rich quintile	21.0 (19.0, 23.1)	21.7 (20.0, 23.6)	21.3 (19.6, 23.1)
Richest quintile	20.1 (18.0, 22.4)	18.4 (16.7, 20.2)	19.7 (17.6, 21.9)
Mother's schooling			
Nil or up to primary	34.3 (31.7, 37.1)	47.6 (45.2, 50.1)	57.9 (55.5, 60.3)
Secondary	43.9 (41.4, 46.4)	40.1 (38.0, 42.2)	34.7 (32.7, 36.7)
Higher secondary	10.9 (9.4, 12.7)	6.9 (6.1, 7.8)	4.9 (3.9, 6.2)
Graduation and above	10.8 (9.3, 12.6)	5.4 (4.7, 6.1)	2.5 (2.1, 3.0)
Father's occupation			
Professional	7.8 (6.8, 8.9)	9.0 (7.9, 10.3)	10.1 (8.6, 11.9)
Sales and services	27.1 (24.8, 29.5)	23.7 (21.7, 25.7)	24.3 (22.6, 26.2)
Manual or agriculture	50.7 (47.9, 53.4)	54.2 (51.6, 56.8)	51.1 (48.6, 53.6)
Others	14.5 (12.4, 16.8)	13.1 (11.5, 14.9)	14.4 (12.5, 16.5)
Drinking water source			
Piped and improved	85.4 (82.8, 87.7)	85.6 (83.3, 87.7)	86.2 (84.2, 87.9)
Nonpiped and improved	8.9 (7.0, 11.2)	8.3 (6.6, 10.3)	8.2 (6.9, 9.8)
Unimproved	5.7 (4.5, 7.2)	6.1 (5.0, 7.4)	5.6 (4.6, 6.8)
Sanitation			
Improved and not shared	43.8 (40.4, 47.3)	40.6 (38.0, 43.2)	48.2 (45.5, 50.8)
Improved and shared	11.5 (10.2, 13.1)	11.7 (10.4, 13.2)	8.8 (7.8, 9.9)
Unimproved	44.7 (40.6, 48.8)	47.7 (44.4, 51.0)	43.1 (40.2, 46.1)
Received IFA in the previous week	7.7 (5.8, 10.1)	10.2 (8.6, 12.1)	9.0 (7.9, 10.3)
Consumption of fish and/or meat			
Never	22.5 (19.9, 25.4)	24.0 (21.9, 26.4)	25.6 (23.3, 28.0)
Occasionally	41.4 (38.5, 44.4)	42.9 (40.0, 45.8)	40.2 (37.9, 42.6)
Weekly once or more	36.0 (33.3, 38.9)	33.1 (30.6, 35.6)	34.2 (31.8, 36.7)
Wasting (based on WHZ for 1–4 y)/thinness (based on BMIAZ for 5–19 y)[2]			
Not present	84.0 (82.1, 85.7)	76.6 (74.9, 78.1)	76.0 (74.1, 77.7)
Moderate	12.4 (11.0, 14.1)	18.3 (16.9, 19.8)	17.5 (16.0, 19.2)
Severe	3.6 (2.8, 4.6)	5.1 (4.3, 6.0)	6.5 (5.7, 7.4)
Stunting (based on HAZ)[2]			
Not present	65.2 (62.8, 67.5)	79.9 (78.2, 81.4)	73.5 (71.4, 75.5)
Moderate	23.0 (21.1, 25.0)	15.2 (13.9, 16.5)	20.8 (19.1, 22.7)
Severe	11.8 (10.3, 13.5)	4.9 (4.2, 5.9)	5.7 (4.9, 6.6)
Underweight (based on WAZ)[2]			
Not present	64.8 (61.9, 67.5)	65.2 (63.2, 67.1)	NA
Moderate	26.4 (23.9, 29.2)	25.1 (23.3, 27.0)	NA
Severe	8.8 (7.6, 10.2)	9.8 (8.7, 10.9)	NA

(*Continued*)

TABLE 1 (*Continued*)

Characteristics	1–4 y	5–9 y	10–19 y
Triceps skinfold thickness-for-age *z* scores[3]			
Low	8.2 (7.0, 9.7)	14.3 (12.9, 15.9)	7.0 (6.0, 8.1)
Normal	91.8 (90.3, 93.0)	83.7 (82.0, 85.2)	88.9 (87.5, 90.2)
Overweight	NA	2.0 (1.5, 2.5)	4.1 (3.2, 5.1)
High serum triglyceride concentrations[4]	NA	33.3 (31.0, 35.7)	16.3 (14.5, 18.2)

[1] Values are means (95% CIs) or percentages (95% CIs). Study sample: participants with serum ferritin and CRP values from the CNNS 2016–18. All analyses were weighted. BMIAZ, BMI-for-age *z* score; CNNS, Comprehensive National Nutrition Survey; HAZ, height-for-age *z* score; IFA, iron–folic acid; NA, not applicable; WAZ, weight-for-age *z* score; WHZ, weight-for-height *z* score.
[2] Not present when *z* score is ≥ −2 SD; moderate when score is −2.1 SD to −3 SD; and severe when it is < −3 SD.
[3] Low when *z* score is <−2 SD; normal when score is −2 SD to +1 SD; and overweight when it is > +1 SD.
[4] High serum triglycerides for 5–9 y is ≥100 mg/dL and for 10–19 y it is ≥130 mg/dL.

Prevalence of ID in relation to age, sociodemographic characteristics, nutritional status, and WASH indicators

The ID prevalence (adjusted for inflammation by the modified BRINDA method) across age groups, when compared between boys and girls by a nonparametric smoothed curve, steadily decreased with age in boys, from >60% at 1 y to <20% at 10 y, followed by a plateau between 10 and 14 y, with further reduction after 14 y (**Figure 3**). For girls, the age-related decline in ID prevalence was observed until ∼8 y followed by an increase in older age groups. Boys had significantly higher ID prevalence than girls until 10 y, but a similar prevalence at ∼11 y, and thereafter a significantly lower prevalence than the girls.

As Table 3 shows, the overall ID prevalence was higher in urban than rural participants and in 1- to 9-y-old children of mothers who had a higher than secondary-level education. In all age groups, participants from the richer households had a higher ID prevalence than those from poorer households. Consistent with this inverse socioeconomic gradient, participants with access to improved sanitation facilities also had a higher ID prevalence.

Stunting and underweight were associated with higher ID prevalence in children <9 y old, but stunted adolescents had lower ID prevalence than their nonstunted peers. Severe thinness, on the other hand, was associated with lower ID prevalence in 5- to 9-y-old children and adolescents (Table 3). In the 1–4 y age group, ID prevalence was significantly lower in children who provided fasting than in those who provided nonfasting samples (25.0% compared with 35.3%), but no significant differences were observed in relation to fasting status in older children and adolescents.

Relation between iron status indicators and inflammation

The prevalence of elevated CRP was higher in children who were from the poorer wealth quintiles, lived in a poor WASH environment, and who were undernourished (**Supplemental Table 3**). However, these associations were statistically robust only in preschool children. Comparison of mean values of ID indicators in children and adolescents with and without inflammation showed significantly higher values of SF and BIS, and lower values of the sTfR/SF index, in participants with inflammation than in those without inflammation, in all age groups. The values of sTfR did not appear to be affected by inflammation (**Supplemental Table 4**).

Exposure associations of iron status indicators

Table 4 and **Supplemental Table 5** summarize the analyses using multiple linear regression models to evaluate the exposure associations of iron status indicators (SF and sTfR). Despite adjustment for CRP, history of fever (2 wk before the survey) had a positive association with SF in the 1–4 y and 5–9 y age groups. Frequent intake of meat and/or fish also had a positive association with SF concentrations in all age groups. A negative association of the wealth index with SF was observed in all age groups despite adjustment for multiple confounders including age; sex; area of residence; mother's education; IFA supplementation; WHZ in the 1–4 y or BMIAZ in the 5–19 y age group; fasting status at blood sampling; intake of meat and/or fish; history of fever and diarrhea; drinking water, sanitation, and handwashing facilities; serum concentrations of CRP and triglycerides; and RBC folate. The association of the wealth index with sTfR was consistent with that observed with SF in preschool children but not in older age groups (Supplemental Table 5). Using ID as a categorical variable with SF and sTfR cutoffs did not materially alter the findings (data not shown).

Interaction of SF with the wealth index as a determinant of hemoglobin

We examined the confounder-adjusted interaction between SF and the wealth index with hemoglobin as a dependent variable to assess iron utilization in different wealth quintiles (Table 5). All adjusted stratified slopes of hemoglobin on SF were significant (except 1 with the poorest wealth index in the 10–19 y age group) and exhibited a downward trend on shifting to poorer wealth index categories.

Discussion

This is the first study from India providing estimates of ID prevalence in a representative sample of children and adolescents at the national and state levels using multiple inflammation-adjusted ID indicators. In preschool children and adolescent girls, ID based on SF adjusted for inflammation by the modified BRINDA method was a public health problem of "moderate" proportions (∼30%–32%), whereas in 5- to 9-y-old children (15%) and adolescent boys (11%) it was a public health problem categorized as "mild" (18). Surprisingly, ID prevalence was higher in richer than in poorer states, in urban than in rural participants, and in participants from richer than from poorer wealth quintiles, despite adjustment for relevant confounders. Groups with high prevalence of

TABLE 2 Estimates of iron indicators and ID in children and adolescents using different methods of inflammation adjustments and ID indicators: Comprehensive National Nutrition Survey 2016–18[1]

	1–4 y			5–9 y			10–19 y		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Adjusted SF (modified BRINDA),[2] μg/L	18.3 (17.8, 18.9)	18.0 (17.4, 18.5)	18.2 (17.8, 18.6)	31.6 (31.0, 32.3)	31.2 (30.5, 31.9)	31.4 (30.9, 32.0)	38.8 (37.9, 39.8)	22.5 (22.0, 23.1)	29.5 (28.9, 30.0)
ID (SF adjusted with modified BRINDA),[2] %	31.5 (30.3, 32.7)	32.4 (31.1, 33.7)	31.9 (31.0, 32.8)	15.3 (14.6, 16.0)	15.7 (15.0, 16.5)	15.5 (15.0, 16.0)	11.5 (10.9, 12.1)	30.4 (29.3, 31.5)	20.9 (20.3, 21.6)
Unadjusted SF, μg/L	19.5 (17.8, 21.3)	19.2 (18.0, 20.5)	19.3 (18.3, 20.4)	31.8 (30.4, 33.3)	31.6 (30.1, 33.2)	31.7 (30.5, 32.9)	39.0 (37.3, 40.7)	23.1 (22.0, 24.2)	30.0 (28.9, 31.1)
ID calculated with different cutoffs if CRP >5 mg/L,[3] %	32.4 (28.8, 36.2)	33.7 (30.6, 37.1)	33.0 (30.7, 35.5)	19.0 (17.2, 20.9)	20.7 (18.5, 23.0)	19.8 (18.3, 21.4)	13.9 (12.3, 15.8)	33.0 (30.3, 35.8)	23.5 (21.9, 25.2)
SF (CRP >5 mg/L excluded),[4] μg/L	18.6 (16.8, 20.6)	17.9 (16.7, 19.2)	18.3 (17.2, 19.4)	30.8 (29.5, 32.2)	30.6 (29.0, 32.3)	30.7 (29.5, 32.0)	38.0 (36.3, 39.8)	22.7 (21.6, 23.8)	29.3 (28.2, 30.4)
ID (CRP >5 mg/L excluded),[4] %	31.4 (27.7, 35.5)	32.5 (29.1, 36.1)	31.9 (29.5, 34.4)	16.3 (14.6, 18.1)	17.2 (15.2, 19.3)	16.7 (15.3, 18.2)	11.3 (9.8, 13.0)	31.0 (28.1, 33.9)	21.3 (19.6, 23.0)
Serum sTfR (CRP >5 mg/L excluded),[5] mg/L	2.33 (2.25, 2.42)	2.30 (2.22, 2.37)	2.32 (2.27, 2.37)	1.87 (1.83, 1.90)	1.83 (1.80, 1.86)	1.85 (1.82, 1.88)	1.68 (1.64, 1.72)	1.89 (1.84, 1.93)	1.78 (1.75, 1.81)
sTfR ≥1.76 mg/L (CRP >5 mg/L excluded),[5] %	75.2 (70.0, 78.1)	73.6 (70.5, 76.5)	74.4 (72.2, 76.5)	55.1 (52.7, 57.6)	51.7 (48.5, 54.9)	53.5 (51.3, 55.6)	41.3 (38.3, 44.5)	52.5 (49.4, 55.6)	47.0 (45.0, 49.0)
sTfR/SF index ≥1.63 (1–4 y) or ≥1.49 (5–19 y) (CRP >5 mg/L excluded),[6] %	53.8 (48.4, 59.1)	50.9 (47.2, 54.6)	52.4 (49.4, 55.4)	32.1 (29.9, 34.4)	31.5 (28.9, 34.2)	31.8 (30.0, 33.6)	21.6 (19.5, 23.8)	40.4 (37.7, 43.3)	31.1 (29.4, 32.9)
BIS <0 mg/kg (CRP >5 mg/L excluded),[7] %	10.7 (9.0, 12.7)	11.6 (9.6, 13.9)	11.1 (9.7, 12.7)	2.2 (1.5, 3.1)	1.7 (1.3, 2.3)	1.9 (1.5, 2.5)	1.4 (0.8, 2.3)	5.9 (4.9, 7.0)	3.6 (3.1, 4.3)
Anemia,[8] %	40.6 (37.6, 43.7)	39.3 (35.9, 42.8)	40.0 (37.7, 42.4)	21.9 (19.6, 24.4)	25.3 (22.4, 28.4)	23.6 (21.6, 25.7)	17.7 (15.8, 19.9)	40.5 (37.5, 43.6)	29.2 (27.4, 31.1)

[1] Values are geometric means (95% CIs) or percentages (95% CIs). Analyses of the study sample (with SF and CRP values): 1–4 y, $n = 9635$; 5–9 y, $n = 11,938$; 10–19 y, $n = 11,507$. BIS, body iron stores; BRINDA, Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia; CRP, C-reactive protein; ID, iron deficiency; SF, serum ferritin; sTfR, serum transferrin receptor.

[2] Estimates after using the probability method of correction for inflammation (modified BRINDA approach). Analysis using SF < 12 μg/L (1–4 y) and <15 μg/L (5–19 y) as ID cutoffs.

[3] For 1–4 y, ID if SF <12 μg/L if CRP ≤5 mg/L, or if SF <30 μg/L if CRP >5 mg/L. For 5–19 y, ID if SF <15 μg/L if CRP ≤5 mg/L, or if SF <70 μg/L if CRP >5 mg/L. 1–4 y, $n = 9635$; 5–9 y, $n = 11,938$; 10–19 y, $n = 11,507$.

[4] Analyses of the subgroup of participants with SF and sTfR values as well as CRP values ≤5 mg/L. 1–4 y, $n = 8511$; 5–9 y, $n = 10,956$; 10–19 y, $n = 10,579$. Analysis using SF <12 μg/L (1–4 y) and <15 μg/L (5–19 y) as ID cutoffs.

[5] Analysis of the subgroup of participants with SF and sTfR values as well as CRP values ≤5 mg/L. 1–4 y, $n = 8511$; 5–9 y, $n = 10,956$; 10–19 y, $n = 10,579$.

[6] sTfR/SF index calculated as sTfR/log-SF (base-10 log). 1–4 y, $n = 8511$; 5–9 y, $n = 10,956$; 10–19 y, $n = 10,579$.

[7] BIS (mg/kg) calculated as −[log10 (sTfR∗1000/SF) − 2.8229]/0.1207. 1–4 y, $n = 8511$; 5–9 y, $n = 10,956$; 10–19 y, $n = 10,579$.

[8] Anemia for 1–4 y, hemoglobin <11 g/dL; for 5–11 y, <11.5 g/dL; for 12–14 y, <12 g/dL; for 15–19 y males, <13 g/dL; and for 15–19 y females, <12 g/dL. 1–4 y, $n = 9635$; 5–9 y, $n = 11,938$; 10–19 y, $n = 11,507$.

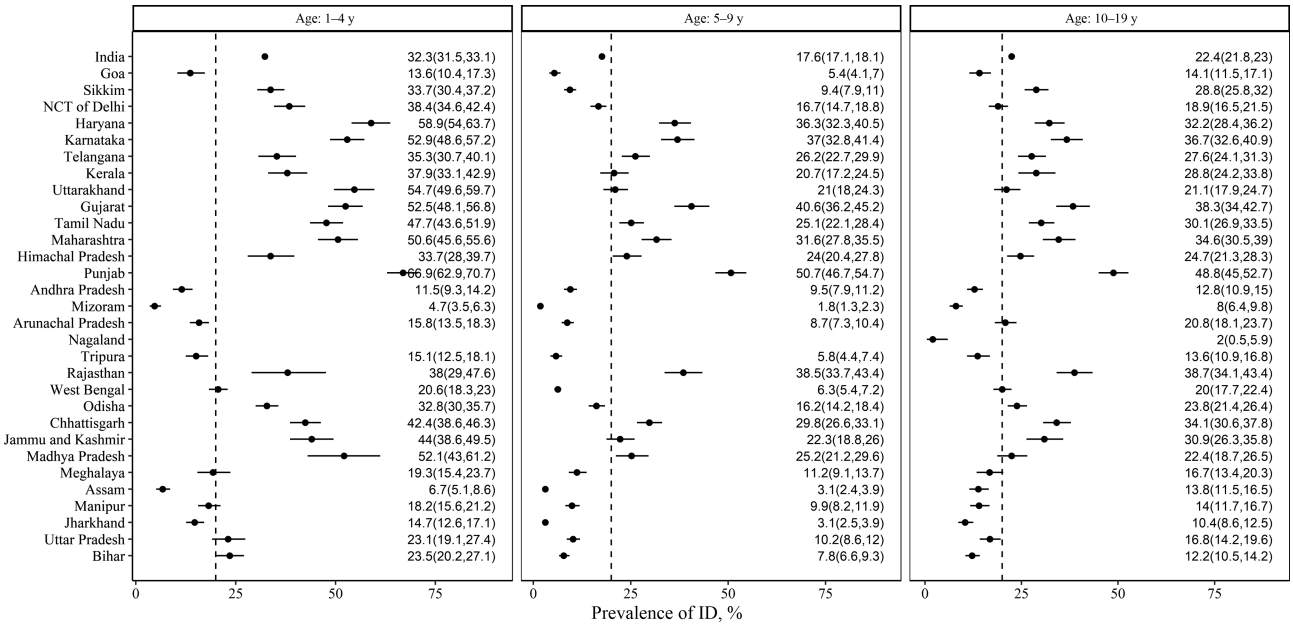

FIGURE 2 Prevalence of ID among children and adolescents (1–19 y) in the states of India: Comprehensive National Nutrition Survey 2016–18. Proportions with 95% CIs estimated after applying the probability method of correction for inflammation (a modified Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia approach). The states are arranged in descending order of per capita net state domestic product. The dotted vertical lines intersecting at 20% prevalence are provided to highlight the threshold of public health significance. Prevalence estimates for 1- to 4-y-old and 5- to 9-y-old children from Nagaland were not computed owing to inadequate sample size. ID, iron deficiency.

inflammation [i.e., those belonging to the poor socioeconomic status (SES) households with unimproved sanitation] had lower ID prevalence, despite different adjustments for serum CRP, especially in the preschool age group. There is some external validity to these findings, because a previous systematic review also reported a relatively lower prevalence of ID in rural than in urban populations; this was attributed to a higher inflammation burden in rural areas (25).

Nevertheless, these intriguing findings need further exploration and our analyses offer important insights on possible reasons. For example, the possibility of a residual effect of unadjusted inflammation cannot be ruled out and our finding that a history of fever was significantly associated with SF, despite adjustment for serum CRP, supports this speculation (Table 4). Only CRP measurements were available in the present study, and its half-life is shorter (26) than α-1-acid glycoprotein (AGP), a relatively long-term indicator of inflammation. The BRINDA study that reviewed cross-sectional data from 16 surveys for preschool children (n = 29,765) found that where both CRP and AGP concentrations were measured, inflammation was substantially higher when defined by elevated AGP (median: 54%) than when defined by elevated CRP (median: 29%) concentrations (27).

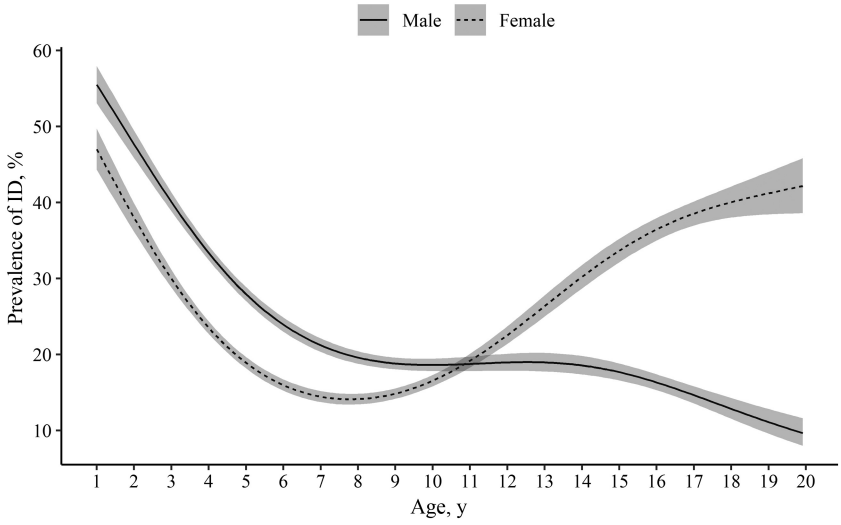

FIGURE 3 Prevalence of ID in male and female children and adolescents in relation to age: Comprehensive National Nutrition Survey 2016–18. Male, n = 17,868; female, n = 15,212. Nonparametric smoothed curve with 95% confidence bands, estimated after applying the probability method of correction for inflammation (a modified Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia approach). ID, iron deficiency.

TABLE 3 ID prevalence by sociodemographic characteristics; indicators of water, sanitation, and hygiene; nutritional status; and grades of anemia in children and adolescents: Comprehensive National Nutrition Survey 2016–18[1]

Characteristics	1–4 y	5–9 y	10–19 y
Residence			
Urban	40.7 (38.8, 42.6)	21.4 (20.1, 22.7)	25.4 (24.1, 26.8)
Rural	28.9 (27.9, 29.9)	13.7 (13.2, 14.3)	19.4 (18.7, 20.1)
Mother's schooling			
Primary	24.1 (21.1, 27.4)	13.6 (12.1, 15.3)	17.9 (16.0, 19.9)
Secondary	33.8 (32.4, 35.2)	14.1 (13.3, 14.9)	20.6 (19.5, 21.7)
Higher secondary	34.4 (31.8, 37.0)	20.2 (18.0, 22.6)	19.6 (17.2, 22.3)
Graduation and above	32.2 (29.6, 34.8)	22.3 (19.8, 25.1)	21.9 (18.2, 25.9)
Wealth index			
Poorest quintile	22.0 (20.2, 23.9)	10.0 (9.1, 10.9)	16.5 (15.2, 17.8)
Poor quintile	24.5 (22.8, 26.2)	10.7 (9.9, 11.6)	16.7 (15.6, 17.9)
Middle quintile	30.4 (28.7, 32.2)	13.0 (12.1, 14.0)	20.8 (19.4, 22.1)
Rich quintile	35.7 (33.8, 37.7)	19.3 (18.0, 20.5)	25.1 (23.6, 26.6)
Richest quintile	43.8 (41.7, 45.9)	25.5 (23.9, 27.1)	24.8 (23.3, 26.3)
Fasting at the time of blood collection			
Nonfasting	35.3 (34.4, 36.3)	16.2 (15.0, 17.4)	19.5 (18.1, 21.0)
Fasting	25.0 (23.7, 26.3)	17.8 (17.3, 18.4)	22.8 (22.2, 23.4)
Fish and/or meat intake			
Never	43.0 (41.2, 44.8)	24.7 (23.5, 25.9)	26.4 (25.2, 27.7)
Occasionally	27.9 (26.8, 29.1)	15.0 (14.3, 15.7)	21.4 (20.5, 22.4)
Weekly once or more	30.2 (29.0, 32.4)	15.8 (15.0, 16.6)	20.5 (19.7, 21.4)
Drinking water source			
Piped and improved	31.6 (30.7, 32.6)	15.6 (15.0, 16.1)	21.3 (20.7, 22.0)
Nonpiped and improved	38.2 (35.2, 41.3)	16.9 (15.1, 18.8)	19.5 (17.6, 21.6)
Unimproved	26.7 (22.6, 31.1)	10.5 (8.6, 12.5)	18.0 (15.3, 21.1)
Sanitation			
Improved and not shared	37.3 (35.9, 38.7)	20.1 (19.2, 21.1)	22.2 (21.3, 23.2)
Improved and shared	31.9 (29.5, 34.3)	16.6 (15.2, 18.1)	22.1 (20.2, 24.2)
Unimproved	26.0 (24.8, 27.3)	11.3 (10.7, 11.9)	19.2 (18.3, 20.2)
Stunting[2]			
Not present	30.0 (29.0, 31.1)	15.3 (14.7, 15.8)	21.4 (20.6, 22.1)
Moderate	31.6 (29.7, 33.5)	16.6 (15.3, 18.0)	21.5 (20.1, 22.9)
Severe	39.6 (36.9, 42.4)	18.0 (15.5, 20.6)	17.0 (14.8, 19.4)
Wasting/thinness[3]			
Not present	31.7 (30.7, 32.7)	15.9 (15.3, 16.6)	22.3 (21.5, 23.1)
Moderate	31.6 (29.2, 34.1)	15.2 (14.0, 16.4)	17.4 (16.0, 18.8)
Severe	27.0 (22.8, 31.5)	12.8 (11.0, 14.8)	17.6 (15.5, 20.0)
Underweight[4]			
Not present	31.1 (30.0, 32.2)	15.5 (14.9, 16.1)	NA
Moderate	31.2 (29.5, 32.9)	15.1 (14.1, 16.1)	NA
Severe	36.1 (33.0, 39.3)	17.5 (15.8, 19.3)	NA
Grades of anemia			
No anemia	20.8 (19.9, 21.8)	13.1 (12.5, 13.6)	13.9 (13.3, 14.5)
Mild anemia	31.3 (29.5, 33.3)	16.5 (14.9, 18.2)	27.3 (25.6, 29.0)
Moderate anemia	69.4 (67.2, 71.6)	25.6 (23.7, 27.5)	51.8 (49.1, 54.5)
Severe anemia	95.1 (92.4, 97.0)	84.9 (76.9, 90.8)	92.5 (88.7, 95.3)

[1] Values are percentages (95% CIs). Estimates of ID using serum ferritin after the probability method of correction for inflammation (modified BRINDA method) with SF <12 μg/L (1–4 y) and <15 μg/L (5–19 y) as ID cutoffs. 1–4 y, $n = 9635$; 5–9 y, $n = 11{,}938$; 10–19 y, $n = 11{,}507$. ID, iron deficiency; NA, not applicable.

[2] Stunting not present when height-for-age z score is ≥ -2 SD; moderate when score is -2.1 SD to -3 SD; and severe when it is < -3 SD.

[3] Wasting (based on weight-for-height z scores) estimated for 1–4 y; thinness (based on BMI-for-age z scores) for 5–19 y. Both not present when z score is ≥ -2 SD; moderate when score is -2.1 SD to -3 SD; and severe when it is < -3 SD.

[4] Underweight not present when weight-for-age z score is ≥ -2 SD; moderate when score is -2.1 SD to -3 SD; and severe when it is < -3 SD. Not estimated for 10–19 y.

Another reason for higher SF values in poorer groups could be the inefficient utilization of stored iron for hemoglobin synthesis, as suggested by a declining trend in the strength of association between hemoglobin and SF from the richest to the poorest wealth quintile (Table 5). Previous reports of similar findings are not available for comparison, but studies have consistently shown lower hemoglobin despite higher SF concentrations in blacks than in whites (28, 29).

TABLE 4 Exposure associations of SF in children and adolescents of the 3 age groups: Comprehensive National Nutrition Survey 2016–18[1]

	1–4 y[2]		5–9 y[3]		10–19 y[4]	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
Age, y	0.22 (0.20, 0.24)	<0.001	0.07 (0.06, 0.08)	<0.001	—	—
Sex						
Male	Reference		—		Reference	
Female	−0.05 (−0.09, −0.01)	0.03	—	—	−0.56 (−0.61, −0.51)	<0.001
Residence						
Urban	Reference		—			
Rural	0.10 (0.05, 0.16)	<0.001	—	—	—	—
Mother's years of schooling	0.01 (0.002, 0.01)	0.01	—	—	0.01 (0.001, 0.02)	0.03
Wealth index						
Richest quintile	Reference		Reference		Reference	
Poorest quintile	0.51 (0.40, 0.61)	<0.001	0.34 (0.28, 0.41)	<0.001	0.41 (0.29, 0.52)	<0.001
Poor quintile	0.39 (0.30, 0.49)	<0.001	0.28 (0.22, 0.34)	<0.001	0.30 (0.21, 0.38)	<0.001
Middle quintile	0.27 (0.19, 0.35)	<0.001	0.21 (0.16, 0.26)	<0.001	0.17 (0.10, 0.24)	<0.001
Rich quintile	0.12 (0.05, 0.19)	0.001	0.13 (0.08, 0.17)	<0.001	0.04 (−0.03, 0.10)	0.26
IFA supplementation in the prior week						
Yes	Reference		Reference			
No	−0.14 (−0.22, −0.06)	0.001	−0.05 (−0.10, −0.004)	0.03	—	—
Fasting at the time of blood collection						
No	Reference		—		—	
Yes	0.27 (0.22, 0.32)	<0.001	—	—	—	—
Frequency of meat and/or fish intake						
Never	Reference		Reference		Reference	
Occasionally	0.25 (0.19, 0.31)	<0.001	0.14 (0.11, 0.18)	<0.001	−0.001 (−0.06, 0.06)	0.97
Weekly once or more	0.32 (0.26, 0.38)	<0.001	0.24 (0.20, 0.28)	<0.001	0.10 (0.04, 0.16)	0.002
Serum CRP, mg/L	—	—	0.04 (0.02, 0.06)	<0.001	0.07 (0.03, 0.10)	<0.001
History of fever 2 wk before survey						
No	Reference		Reference			
Yes	0.27 (0.23, 0.32)	<0.001	0.20 (0.16, 0.23)	<0.001	—	—
History of diarrhea 2 wk before survey						
No	—		Reference		—	
Yes	—	—	−0.09 (−0.14, −0.04)	<0.001	—	—
Log RBC folate, ng/mL	−0.04 (−0.07, −0.01)	0.01	0.11 (0.10, 0.13)	<0.001	0.05 (0.02, 0.07)	0.001
Log triglycerides, mg/dL	—	—	0.18 (0.15, 0.22)	<0.001	0.18 (0.13, 0.23)	<0.001
Sanitation facilities						
Improved and not shared			Reference			
Improved and shared	—	—	0.02 (−0.03, 0.07)	0.48	—	—
Unimproved	—	—	0.07 (0.03, 0.11)	0.001	—	—
Handwashing facilities						
Basic	—		Reference			
Limited	—	—	0.07 (0.04, 0.11)	<0.001	—	—
No facilities	—	—	0.12 (0.08, 0.17)	<0.001	—	—
R^2	0.163		0.134		0.153	

[1] Values are unstandardized regression β coefficients (95% CIs) unless otherwise indicated. Analyses of the subgroup of participants with SF and sTfR values as well as serum CRP values ≤5 mg/L: 1–4 y, $n = 8511$; 5–9 y, $n = 10,956$; 10–19 y, $n = 10,579$. Estimates of multiple linear regression analyses with exposure variables selected from the last step of the backward stepwise regression and adjusted for CRP (also adjusted for censoring of CRP measurements). SF, serum retinol, serum vitamin B-12, RBC folate, and serum triglycerides were log transformed before analyses. CRP, C-reactive protein; IFA, iron–folic acid; SF, serum ferritin.
[2] In addition adjusted for weight-for-height *z* score, source of drinking water, and sanitation.
[3] In addition adjusted for BMI-for-age *z* score and source of drinking water.
[4] In addition adjusted for handwashing facilities.

Those authors attributed this to a reduced iron mobilization from stores for hemoglobin synthesis due to poor nutrition and health. As observed elsewhere in low-SES participants, a higher inflammation burden with poor diet quality and low intake of high-quality protein and other hematopoietic nutrients may preclude efficient iron utilization from ferritin (30). This "functional iron deficiency" despite available iron stores in children from poorer households requires a deeper mechanistic enquiry (31). Serum hepcidin measurements would have been useful here, because an increase in hepcidin due to inflammation would impair the mobilization of iron stores (32).

The ID prevalence in our study was lower than that estimated in previous scattered and not nationally representative Indian reports in comparable age groups (33–35). In the absence of representative data on ID, strengthening the universal IFA supplementation program along with other approaches like food fortification has been the invariable policy response to the

TABLE 5 Adjusted slope of hemoglobin on SF at different wealth quintiles estimated by linear interaction model in children and adolescents of the 3 age groups: Comprehensive National Nutrition Survey 2016–18[1]

	1–4 y[2]		5–9 y[3]		10–19 y[4]	
Variables	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
SF at richest quintile	0.031 (0.026, 0.035)	<0.001	0.005 (0.003, 0.007)	0.004	0.013 (0.011, 0.016)	<0.001
SF at richer quintile	0.017 (0.014, 0.020)	<0.001	0.008 (0.006, 0.010)	<0.001	0.018 (0.015, 0.021)	<0.001
SF at middle quintile	0.017 (0.014, 0.020)	<0.001	0.006 (0.005, 0.008)	<0.001	0.006 (0.003, 0.008)	<0.001
SF at poor quintile	0.020 (0.017, 0.022)	<0.001	0.004 (0.002, 0.006)	<0.001	0.004 (<0.001, 0.007)	0.03
SF at poorest quintile	0.010 (0.008, 0.013)	<0.001	0.004 (0.002, 0.005)	<0.001	−0.001 (−0.001, 0.01)	0.73
R^2	0.269		0.118		0.316	

[1]Values are unstandardized regression coefficients/adjusted slope βs (95% CIs) unless otherwise indicated. Estimates were derived from multiple linear regression models of the study sample with interaction terms of SF with the wealth index and adjusted for confounders selected from the last step of the backward stepwise regression and CRP (also adjusted for censoring of CRP). 1–4 y, $n = 9635$; 5–9 y, $n = 11{,}938$; 10–19 y, $n = 11{,}507$. Serum retinol, serum vitamin B-12, RBC folate, and serum triglycerides were log transformed before analyses. CRP, C-reactive protein; SF, serum ferritin.

[2]Adjusted for age, history of fever in the last 2 wk, serum retinol, RBC folate, serum vitamin B-12, weight-for-height *z* scores, CRP, mother's schooling, frequency of meat and/or fish intake, drinking water source, fasting status, handwashing, and sanitation.

[3]Adjusted for age, history of diarrhea in the last 2 wk, history of fever in the last 2 wk, serum retinol, RBC folate, BMI-for-age *z* scores, CRP, sanitation, and frequency of meat and/or fish intake.

[4]Adjusted for age, sex, area of residence, serum retinol, RBC folate, serum vitamin B-12, CRP, mother's schooling, frequency of meat and/or fish intake, drinking water source, and sanitation.

high anemia burden in India. However, the possible inefficient utilization of stored iron for hemoglobin synthesis in children from lower wealth quintiles suggests that iron supplementation alone may be of limited value, and the focus should be on improved diet diversity, which facilitates iron absorption while providing all other hematopoietic nutrients. Earlier analyses from India have shown a weak association between dietary iron intake and anemia (36) and have also suggested lower content for iron fortification based on the average iron requirement (37).

We found wide variations in the estimated ID prevalence using different indicators (Table 2). A similarly wide variation has been reported by previous studies (5) and is not surprising because these ID markers reflect different metabolic processes (38). SF concentrations decrease with decreasing iron stores but are insensitive to further change during severe ID. The sTfR concentration, however, starts rising after the depletion of iron stores and its increase is proportionate to the tissue iron deficit (38). However, our finding of a higher ID prevalence estimated by sTfR than by SF criteria is inconsistent, because the depletion of iron stores is likely to precede tissue ID. This discrepancy may be related to the cutoffs of SF and sTfR used in the diagnosis of ID (the SF cutoff was perhaps too stringent, or the sTfR cutoff was not stringent enough, or both), as also noted in a previous study (39). The recommended SF cutoffs may have high specificity but low sensitivity, as reported by a study in Malawian children which found 90% specificity and 45% sensitivity of inflammation-adjusted SF concentration <12 mg/L against bone marrow iron (8, 40). The sTfR concentrations were unaffected by inflammation in our study, similar to some (41) but not all (42) reports. The lack of assay standardization and nonavailability of common reference ranges for sTfR, however, compromise its utility to evaluate population iron status (38). Owing to reasons of cost, practicality, and response to iron intervention, SF is the most commonly used ID indicator and is useful for comparisons across different studies (18).

The strong positive association of frequent (weekly once or more) animal source food (meat and/or fish) intake with SF is expected because of the higher bioavailability of heme iron (43). However, the high prevalence of elevated triglyceride concentrations in school-age children and its positive association with SF are disconcerting. A positive association of SF with metabolic syndrome and its components, especially elevated serum triglycerides, has been reported in adults (44), as well as children and adolescents (45, 46). The underlying mechanisms may include oxidative stress related to high iron concentrations resulting in insulin resistance and endothelial damage or an increase in SF due to inflammation associated with hypertriglyceridemia (47).

The strengths of our study include a large sample, representative at state and national levels, covering a wide age range of 1–19 y, along with information on the inflammation-adjusted ID prevalence estimates derived using different indicators of ID. An important limitation includes the lack of AGP measurements, which may have resulted in incomplete adjustment for inflammation (48). A lower proportion of 1- to 2-y-old children may also have resulted in underestimation of ID in the 1–4 y age group.

In conclusion, the ID prevalence in a large nationally representative sample of Indian children and adolescents shows that about one-third of the preschool children and adolescent girls are likely to be iron deficient. In 5- to 9-y-old children and adolescent boys, the prevalence is even lower (11%–15%). Although underestimation of ID prevalence due to incomplete adjustment for inflammation is a possibility, this subset is unlikely to be amenable to iron interventions owing to elevated serum hepcidin (49). Future studies on ID prevalence should include hepcidin measures to aid interpretation of findings. In view of persistent inflammation, withholding IFA supplementation for 2 wk after febrile illness may be useful during IFA interventions. Our findings have important implications for iron supplementation and fortification programs. An important conclusion is that given the impaired iron utilization for hemoglobin synthesis in low-SES children, intended benefits on anemia will not accrue if iron intake is increased without also addressing the multiple environmental constraints related to poverty. In addition, targeted anemia control strategies may need to be considered to maximize the benefits of IFA supplementation while reducing unintended harms.

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data interpretation; R Pullakhandam, GBR, RJ, PKA, ADW, AVK, and HSS: contributed to the data interpretation and reviewed the manuscript; HSS, UK, HR, and AK: served as technical experts on micronutrient deficiencies and reviewed the paper; SD: guided the survey implementation and policy implications; and all authors: read and approved the final manuscript.

Data Availability

The Ministry of Health and Family Welfare (MoHFW), Government of India, owns the CNNS data. Data used in this article will be made available by the MoHFW.

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